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Documentation, supplement – Translation of the German version from 2019**

Hartwig, Andrea ; MAK Commission ; et al ; Arand, Michael

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α -Aluminium oxide (corundum) (respirable fraction)

MAK Value Documentation, supplement - Translation of the German version from 2019

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Keywords

alpha-aluminium oxide, lung, toxicity, general threshold limit value for dust, maximum workplace concentration, MAK value, carcinogenicity, hazardous substance

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated α -aluminium oxide [1344-28-1]. α -Aluminium oxide is a biopersistent granular dust. There are no inhalation studies from which a NOAEC could be derived. Therefore, the respirable fraction of α -aluminium oxide dust is classified in Carcinogen Category 4 and a maximum concentration at the workplace (MAK value) of $0.3 \text{ mg/m}^3 \times \text{material density}$ is established for the respirable fraction by analogy with the other biopersistent granular dusts (GBS). As workers are generally exposed to several aluminium species at the workplace, it is recommended that the biological tolerance value (BAT value) for aluminium is also observed. The classification in Carcinogen Category 4 is based on data that showed increased tumour incidences in rats exposed to biopersistent granular dusts in the high dose range. These tumours are regarded as a consequence of the inflammatory mechanism of action, for which a threshold can be defined. Direct genotoxic effects appear to be of subordinate relevance for the carcinogenicity of biopersistent granular dusts. By analogy with biopersistent granular dusts, Peak Limitation Category II is established for α -aluminium oxide with an excursion factor of 8. Since α -aluminium oxide is not systemically distributed and accumulates only locally in the lungs, damage to the embryo or foetus is unlikely when the MAK value or the BAT value is not exceeded. α -Aluminium oxide is classified accordingly in Pregnancy Risk Group C. α -Aluminium oxide is not expected to be a sensitizer and is not taken up via the skin in toxicologically relevant amounts.

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MAK value (2018)	0.3 mg/m³ R × material density^{a)}
Peak limitation (2018)	Category II, excursion factor 8
Absorption through the skin	–
Sensitization	–
Carcinogenicity (2018)	Category 4
Prenatal toxicity (2018)	Group C
Germ cell mutagenicity	–
BAT value (2017)	50 µg aluminium/g creatinine in urine
EINECS number	215-691-6
CAS number	1344-28-1, 1302-74-5
Molecular formula	Al ₂ O ₃
Molar mass	101.96 g/mol
Melting point	2045 °C (IFA 2018)
Density at 20 °C	3.99 g/cm ³ (IFA 2018)
Mohs' hardness	6.5–9.0 (IFA 2018)
Solubility	insoluble in water, acids and bases (IFA 2018)

^{a)} The effect of α -aluminium oxide is based on the effect of biopersistent granular dusts. The MAK value of 0.3 mg/m³ for the respirable fraction applies to a material density of 1 g/cm³.

Note: Evaluation except for aluminium oxide fibres and ultrafine particles; see section V h of the List of MAK and BAT Values

This supplement evaluates only insoluble corundum (α -aluminium oxide) on the basis of findings from studies published since the 2007 supplement (Hartwig 2013). This compound differs from the soluble aluminium compounds with respect to its bioavailability and translocation in the body after exposure. It therefore has a different mechanism of action and induces different effects. Other aluminium oxide modifications such as γ -Al₂O₃ differ markedly from the α modification with respect to their physico-chemical properties. The CAS number 1344-28-1 applies to both forms of aluminium oxide (alpha and gamma).

General information

Extraction and production of corundum

In addition to various processes for culturing single crystals, synthetic corundum is generally produced from the raw material bauxite for industrial applications. So-called brown fused alumina (electrocorundum) is produced in electric arc furnaces and has a purity of about 96%. Another method used to refine bauxite for the production of aluminium oxide is the Bayer process; the product is then converted to what is known as white fused alumina (purity > 99%) in electric arc furnaces (Holleman et al. 2007).

Aluminium oxide occurs naturally in large deposits as corundum. In impure form with admixtures of iron oxide and quartz, it is found also as emery. Al_2O_3 is produced in the laboratory as the modification $\gamma\text{-Al}_2\text{O}_3$, which does not occur naturally, by cautious heating of hydrargillite ($\text{Al}(\text{OH})_3$) or boehmite ($\text{AlO}(\text{OH})$). At temperatures above 1100°C , $\gamma\text{-Al}_2\text{O}_3$ is irreversibly converted into the hexagonal, thermodynamically stable $\alpha\text{-Al}_2\text{O}_3$ (corundum), which is insoluble in water, acids and bases (Römpf 2013).

Surface oxidation of aluminium

In general, aluminium reacts with oxygen in the air, forming a passivating oxide layer on its surface. Oxide layers with a thickness of 5 to $25\mu\text{m}$ can be produced technically in an electrolyte solution by a direct current (Eloxal process) or an alternating current (WX process). Neither the naturally occurring nor technically produced oxide layers are corundum (Holleman et al. 2007).

Applications

Corundum is used for the production of oxide ceramics, abrasives, blasting abrasives and polishing agents or as an aggregate for the production of fireproof materials. In this context, corundum is also used to make fireproof linings for blast furnaces or for structural ceramics (valves, crucibles, etc.) and casting dies. Very finely ground corundum with a particle size of about 100 nm is used for the production of scratch-resistant varnishes. Further application areas are the production of artificial gemstones (rubies, sapphires) and its use as a substrate for catalysts. As a result of its hardness, corundum continues to be used for the production of hard concretes and is made into jewels for watches and electrical measuring devices (Römpf 2013).

Exposure

Exposure specifically to aluminium occurs primarily during the production of aluminium powder and at aluminium welding workplaces. This can lead to exposure by inhalation to respirable aluminium dusts and to aluminium fumes. Exposure to aluminium may naturally also involve exposure to corundum, however slight this may be. For this reason, the studies below are included in this supplement:

In studies of particle size fractions in the steel and aluminium welding industry, mass median aerodynamic diameters (MMAD) ranging from 1.5 to $>20\mu\text{m}$ were determined during three different welding operations. The MMAD of particles produced during tungsten inert gas welding was found to be $1.7 \pm 1.6\mu\text{m}$, $1.5 \pm 7.5\mu\text{m}$ during metal inert gas welding and $>20 \pm >20\mu\text{m}$ during resistance spot welding. X-ray diffraction analysis of the airborne dusts from welding workstations revealed that a complex mixture of particles was present in the air. The fraction with an MMAD of $>20\mu\text{m}$ was primarily made up of silicon, aluminium, calcium and iron, while the fraction with an MMAD of $1\mu\text{m}$ contained carbon, magnesium, silicon, chromium, iron and aluminium. The particle concentration in the $1\mu\text{m}$ -fraction was $72\,000\text{ particles/cm}^3$ (range: $45\,000\text{--}130\,000\text{ particles/cm}^3$). The authors reported that exhaust systems removed 90% of the particles from the air. However, they did not remove the particle fractions with an MMAD of $>20\mu\text{m}$ and $<0.05\mu\text{m}$ (Dasch and D'Arcy 2008).

In the United States, levels of aluminium in the air ranged from $0.005\mu\text{g/m}^3$ to $0.18\mu\text{g/m}^3$ depending on the location, weather conditions and distance from industrial sites. In contrast, aluminium levels in urban and industrial areas can range from 0.4 to $8.0\mu\text{g/m}^3$. Most of the aluminium in the air is particle bound (ATSDR 2008).

A study investigated exposure to aluminium in a shipyard and at an aluminium sulfate manufacturing company. The airborne particles were analysed by X-ray diffraction and scanning electron microscopy. Mainly metallic aluminium and aluminium oxide were detected at the welding workstations of the shipyard. The total dust concentration was 3.5 mg/m^3 (range: $0.3\text{--}13.6\text{ mg/m}^3$); aluminium constituted 32% of the total dust mass at an average concentration of 1.1 mg/m^3 (range: $0.008\text{--}6.1\text{ mg/m}^3$) (Riihimäki et al. 2008).

In a Polish aluminium foundry, the aluminium levels at workstations in the smeltery, locksmith's workshop and in the saw mill were determined by personal air sampling. The workers were exposed to aluminium oxide. The temperatures necessary to form corundum are generally not reached at aluminium foundries. However, exposure to corundum cannot be ruled out. The aluminium concentrations determined at the workstations were $0.32 \pm 0.18 \text{ mg/m}^3$ (casting smelters), $0.41 \pm 0.18 \text{ mg/m}^3$ (locksmiths) and $0.61 \pm 0.63 \text{ mg/m}^3$ (sawyers and auxiliary workers) (Halatek et al. 2006).

1 Toxic Effects and Mode of Action

Corundum is insoluble in water and biological liquids and is thus biopersistent. The granular particles of this compound induce the same effects as other biopersistent granular dusts. The particles can accumulate in the lungs and lymph nodes, impair lung function and overload lung clearance (Hartwig 2014).

The findings of epidemiological and animal studies revealed that the primary target organ of corundum particles after exposure by inhalation is the lungs. Particles of insoluble aluminium oxide can accumulate in the lungs at high concentrations and impair lung clearance, which—in addition to lung clearance overload—can result in the development of aluminosis.

Aluminosis is a form of diffuse interstitial lung fibrosis, which is mainly manifest in the upper and middle lung fields and can lead to subpleural emphysema blebs and spontaneous pneumothorax at an advanced stage (see Hartwig 2013); although this is more likely in the case of bioavailable aluminium compounds than in the case of corundum itself. Aluminosis is characterized by the formation of dense connective tissue with few cells and large amounts of collagen fibres with a high shrinkage tendency. This may result in lung shrinkage with hyaline thickening of the alveolar septa, and in some cases obliteration of the alveolar lumen and atrophy of the respiratory epithelium (BAuA 2009).

“Shaver’s disease” is a special form of lung fibrosis (Hunter 1975; Valentin et al. 1985; Worth and Schiller 1954). Earlier studies reported that Shaver’s disease occurred only in workers who were exposed to gases released during the smelting process and not in workers who were exposed only to corundum dusts (Worth and Schiller 1954). This indicates that the disease cannot be attributed to corundum itself, but to co-exposure during the smelting process.

Soluble aluminium compounds may lead to neurotoxic effects (Hartwig 2013); however, because of the high degree of biopersistence, it is unlikely that inhaled corundum reaches the blood and the brain and induces toxic effects there.

Studies have not been carried out to investigate fertility disorders induced by insoluble aluminium oxide (see Hartwig 2013).

There is insufficient evidence for the induction of skin sensitizing effects in humans by corundum and no animal studies are available. There is no evidence for the induction of sensitizing effects on the airways.

2 Mechanism of Action

After exposure by inhalation, the granular particles of corundum induced the same effects as biopersistent granular dusts (see Hartwig 2014).

Therefore, chronic inhalation exposure to corundum particles can lead to the accumulation of dust particles in the lungs and lymph nodes, impairment of lung function, clearance overload, inflammatory changes in the lungs and fibrosis.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

As a result of its insolubility, corundum is not absorbed after inhalation, but is instead removed by different clearance mechanisms. Particles that have reached the lower respiratory tract are eliminated by macrophage-mediated clearance. The further translocation of the particles follows the same mechanism as for biopersistent granular dusts (Hartwig 2014).

3.2 Metabolism

There are still no data available. As corundum is inert, it is not expected to be subjected to any metabolic process.

4 Effects in Humans

4.1 Single exposures

There are no new data available.

4.2 Repeated exposure

A study from 1947 reported the occurrence of lung disease in 23 workers of a plant manufacturing corundum. The workers had been employed at the plant for 23 months to 15 years. They were exposed to fumes containing aluminium oxide, silica and small quantities of other substances. They had symptoms such as dyspnoea, pneumothorax and diffuse irregular shadows on the lungs, which rapidly progressed into fibrosis. The study did not provide detailed exposure data (Krewski et al. 2007).

The aluminium concentrations in the urine and blood and the club cell protein concentrations, which the authors described as a sensitive biomarker for respiratory diseases, and hyaluronic acid in serum were determined in 66 male workers (50 casting smelters, 5 locksmiths, 11 sawyers and auxiliary workers) of a Polish aluminium foundry and in 42 control persons not exposed. The aluminium concentrations at the workstations were determined by personal air sampling. The workers were exposed also to aluminium oxide; however, the presence of the corundum modification was not identified analytically. The dust concentration was determined as “total dust”. The aluminium concentration in the dust was determined by atomic absorption spectrometry. The authors found a correlation between the Al_2O_3 concentration and the dust concentration. In addition, a pulmonary function test was carried out for each worker to determine the FVC (forced volume capacity), FEV_1 (forced expiratory volume in 1 second), $\text{FEV}_1\%$ (Tiffenau index, FEV_1/FVC) and FEF_{50} (forced expiratory flow at 50% of vital capacity) and the workers were asked about their smoking habits. The number of persons who had never smoked was below 42% (smelters: 30.6%, locksmiths: 40%, sawyers and auxiliary workers: 41.7%, controls: 26.2%). The aluminium concentrations at the workstations were $0.32 \pm 0.18 \text{ mg/m}^3$ (smelters), $0.41 \pm 0.18 \text{ mg/m}^3$ (locksmiths) and $0.61 \pm 0.63 \text{ mg/m}^3$ (sawyers and auxiliary workers), respectively. The lowest FEV_1 , $\text{FEV}_1\%$ and FEF_{50} values were found in the locksmiths; this was, however, the group with the oldest workers. A comparison of the pulmonary function values of the smelters, sawyers and auxiliary workers revealed a correlation between the deterioration in lung function and the level of toxic substances in the air. In addition, when compared with the control persons, the smelters were found to have a significantly higher aluminium concentration in the urine at $43.7 \pm 23.7 \text{ } \mu\text{g/l}$, significantly higher superoxide dismutase activity and a significantly higher myeloperoxidase concentration, a significantly lower club cell protein concentration and a not significant increase in glutathione S-transferase activity. After adjusting for the confounding variables smoking and age, the findings revealed that, on the one hand, there is a significant negative correlation between the aluminium concentration in the urine and the FVC and FEV_1 and, on the other hand, the aluminium

concentration in serum is negatively correlated with the club cell protein concentration in serum. As it is likely that the concentrations found in the urine and blood of the subjects were bioavailable aluminium species, the findings cannot be used to evaluate corundum (Hałatek et al. 2006).

In Sudan, 50 male workers who were exposed to dust containing aluminium for 8 hours per day for a period of employment lasting at least one year (maximum 10 years) were investigated for atypical cytological changes in the lungs. The publication used the term mineral dust as a general term for iron and aluminium dusts. The study does not provide data for aluminium compounds and their concentrations in the dust. The control group was made up of 157 office workers who were not exposed to dust. The group of workers exposed to aluminium dust included 13 smokers, the control group 39 smokers. The demographic variables were determined by questionnaire. Two sputum samples per person were collected on 2 consecutive days and swabs were taken. Cell dysplasia was not observed in any of the workers who were exposed to aluminium dust; however, there was 1 case of squamous cell metaplasia among the workers and 10 cases (6%) among the control persons. In addition, a viral infection was diagnosed in 1 aluminium worker and in 8 (5%) control persons (Ahmed et al. 2013).

Two cases were described based on the assumption that corundum is produced during aluminium welding processes: a 43-year-old worker was examined who had first worked in a shipyard for 16 years, grinding down welding seams. This was followed by 8 years of actual work as a welder. A handkerchief that the worker tied around his face provided the only protection. He smoked 4 cigarettes per day for 5 years. Chest X-rays revealed a 10% left pneumothorax. Severe fibrotic lung disease developed at this time. A pulmonary function test demonstrated an FVC of 46%. The worker was diagnosed clinically with stage III sarcoidosis (Hull and Abraham 2002).

A second case, a 45-year-old colleague, had worked for 22 years as an aluminium welder, also without sufficient respiratory protection. Also this patient was a smoker. Marked dyspnoea prevented him from engaging in physical exercise. The FVC was 77% of the normal value, and polycythaemia was determined. Inoperable lung tumours developed after several years (Hull and Abraham 2002).

4.3 Local effects on skin and mucous membranes

There are no new data available.

4.4 Allergenic effects

There are no data for the sensitizing effects of corundum.

There is only one report of a probable allergic reaction to aluminium oxide (no other details) in a worker who developed contact dermatitis on his hands and forearms after grinding marble with an aluminium oxide-based abrasive medium. In the patch test, the worker reacted strongly to the aluminium of the test chambers. Another patch test carried out with plastic chambers yielded a 2+ reaction also to 1% and 2% aluminium chloride in petrolatum or water (Tosti et al. 1990). It was not clear whether the sensitization was caused by exposure to aluminium oxide or by exposure to other forms of aluminium or aluminium salt.

4.5 Reproductive and developmental toxicity

There are no new data available.

4.6 Genotoxicity

There are no new data available.

4.7 Carcinogenicity

Cohort studies

The studies below are described only because corundum may have been produced during these work processes (see Section 4.2). A cohort study investigated 5828 male workers in bauxite mines and aluminium refineries in Australia, who were divided into the groups “office”, “maintenance” and “production” depending upon their occupation, and by length of employment. The study did not provide any details for the aluminium species and their concentration in dust. The aluminium compound and other substances that the workers were exposed to and the level of exposure cannot be determined from the study data. The mortality levels from all causes and from circulatory and respiratory diseases, all cancers and injury were lower in the workers than in the Australian male population; this finding can be attributed to the healthy worker effect. The incidence of all cancers combined was not increased. The only significantly increased mortality risk was for pleural mesotheliomas (SMR = 2.84, 95% CI: 1.18–6.83). The incidences of mesotheliomas (SIR = 3.49, 95% CI: 1.82–6.71) and melanomas (SIR = 1.30, 95% CI: 1.00–1.69) were increased. According to the authors, the melanomas were probably caused by high-level exposure to the sun and the mesotheliomas were probably caused by exposure to asbestos in addition to the exposure to aluminium. Incomplete data were provided for exposure and for the confounder smoking (Fritschi et al. 2008).

The mortality data for 5770 male workers from four bauxite mines and 3 aluminium refineries in Australia were analysed; the data were collected in the period between 1983 and 2002. Office workers in the respective companies were used as controls. Of the interviewed persons, 40% were non-smokers, 27% former smokers and 27% smokers. The smoking status of 5% of the volunteers could not be determined. The mine workers (57%) were exposed to bauxite concentrations of 5.7, 13.4, 17.0 and 187 mg/m³ × year (median, mean, interquartile range, maximum), the refinery workers (41%) to aluminium concentrations of 2.8, 14.5, 13.9 and 210 mg/m³ × year. In the workers exposed to bauxite, the increase in the mortality risk for cerebrovascular disease (RR 2.1, 95% CI: 0.5–8.1, n = 10) and for non-malignant respiratory diseases (RR 5.8, 95% CI: 0.6–1.4, n = 79) was not significant, whereby the correlation between the latter and bauxite exposure was positive and significantly monotonic. An increased mortality risk for cerebrovascular diseases (RR 3.8, 95% CI: 1.1–13, n = 10) was determined for the workers exposed to aluminium. The authors noted that an association between aluminium exposure and cerebrovascular diseases was observed only when the exposed persons were compared with the control persons of this study, but not when they were compared with external controls. As it can be assumed that the cerebrovascular damage is more likely associated with bioavailable aluminium species, this finding cannot be included in the evaluation of corundum (Friesen et al. 2009).

Another study investigated a cohort of 4396 male workers from aluminium smelters in Australia. The workers were divided into the groups “production”, “maintenance” and “office”, and by length of employment. The aluminium compound that the workers were exposed to and the level of exposure cannot be determined from the study data. Incomplete data were provided for the confounder smoking. Significantly reduced mortality levels were determined for all causes and for all cancers combined; this can be attributed to the healthy worker effect. There was a significant increase in the mortality levels for mesotheliomas (SMR = 3.52, 95% CI: 1.47–8.46) and the incidences were increased for stomach cancer (SIR = 1.95, 95% CI: 1.16–3.29), mesotheliomas (SIR = 2.41, 95% CI: 1.00–5.78), urinary tract cancer (SIR = 1.45, 95% CI: 1.01–2.17) and kidney cancer (SIR = 1.99, 95% CI: 1.12–3.35). The incidence risk was significantly reduced for melanomas (SIR = 0.60, 95% CI: 0.39–0.94) and for colorectal carcinomas (SIR = 0.65, 95% CI: 0.44–1.00). The authors attributed the increased mesothelioma risk to earlier exposure to asbestos (Sim et al. 2009).

Summary

The carcinogenic potential of corundum cannot be evaluated on the basis of the epidemiological data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

There are no new data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Intratracheal application of amorphous particles from a corundum furnace induced mild lung fibrosis in rats. The particle sizes ranged from 0.02 to 0.5 μm (no other details, Krewski et al. [2007](#)).

5.2.2 Oral administration

There are no new data available.

5.2.3 Dermal application

There are no new data available.

5.3 Local effects on skin and mucous membranes

There are no new data available.

5.4 Allergenic effects

There are no data available for the sensitizing effects of corundum.

A local lymph node assay, which was carried out according to OECD Test Guideline 429 in female CBA/J mice with 10%, 25% and 50% formulations of a mixture of aluminium oxide, cerium dioxide and magnesium oxide in propylene glycol that was doped with terbium, yielded stimulation indices of 1.9, 1.7 and 1.8, respectively, and thus negative results (ECHA [2018 a](#)).

A maximization test carried out with aluminium hydroxide in male Dunkin Hartley guinea pigs (intradermal induction: 1%, topical induction: 100%, challenge treatment: 75% and 37.5% aluminium hydroxide in a 1% methyl cellulose formulation) did not yield a reaction in any of the 10 animals (ECHA [2018 b](#)).

5.5 Reproductive and developmental toxicity

There are no new data available.

5.6 Genotoxicity

There are no new data available.

5.7 Carcinogenicity

There are no new data available.

6 Manifesto (MAK value/classification)

Corundum is insoluble, biopersistent and not bioavailable. The granular particles do not cause a specific form of toxicity, but induce the same effects as other biopersistent granular dusts.

MAK value. Corundum causes lung fibrosis after exposure by inhalation at high concentrations (Hartwig 2013; Henschler 1991).

In studies of workers who were diagnosed with lung fibrosis (aluminosis), the aluminium concentrations in the urine were higher than the BAT value of 50 $\mu\text{g/g}$ creatinine. As corundum is insoluble, the findings in the urine are attributed to soluble aluminium species. A dose–response relationship cannot be determined at present because too little exposure data are available for the development of aluminosis. However, after considering the biomonitoring values and the case reports, it is to be assumed that very high levels of exposure far above the limit value of $0.3 \text{ mg/m}^3 \times \text{material density}$ over a period of many years are required. Previously published epidemiological and animal studies of dusts containing corundum did not provide any evidence of adverse health effects other than those determined for biopersistent granular dusts. For this reason, a MAK value of $0.3 \text{ mg/m}^3 \times \text{material density}$ of the substance has been established by analogy for the respirable fraction.

As workers are generally exposed to several aluminium species at the workplace, the BAT value for aluminium must be observed.

Peak limitation. The effects on the lungs are critical. For this reason, the respirable fraction of corundum has been classified in Peak Limitation Category II, like other biopersistent granular dusts. As the clearance half-life of biopersistent granular dusts is about 400 days, an excursion factor of 8 has been established.

Prenatal toxicity. There are no studies of developmental toxicity available for corundum. As corundum dust is not readily soluble, prenatal toxicity is not to be assumed after exposure at the MAK value. Corundum has been classified in Pregnancy Risk Group C also in analogy to biopersistent granular dusts.

Carcinogenicity. As corundum is a biopersistent granular dust, particle-induced tumours may develop at high concentrations. This is mainly caused by inflammation in the alveolar and bronchial regions, which is accompanied by the release of reactive oxygen species. For this reason, the respirable fraction of corundum has been classified in Carcinogen Category 4 in analogy to other biopersistent granular dusts.

Germ cell mutagenicity. There are no data available for genotoxicity. However, this is not to be expected by analogy to other biopersistent granular dusts. For this reason, corundum is not classified in one of the categories for germ cell mutagens.

Absorption through the skin. There is no evidence that corundum is absorbed through the skin. Therefore, in analogy to other biopersistent granular dusts, corundum has not been designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are too few clinical findings in humans and no positive results in animal studies for the sensitizing effects of corundum or other aluminium oxide modifications on the intact skin. There is also no evidence that corundum has sensitizing effects on the airways. Therefore, corundum is not designated with either “Sh” or “Sa” (for substances which cause sensitization of the skin or airways).

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